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Effects of IGF-I on renal function in end-stage chronic renal failure

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Effects of IGF-I on renal function in end-stage chronic renal failure. To determine whether insulin-like growth factor I (IGF-I) affects kidney function in patients with end-stage chronic renal failure, we administered recombinant human IGF-I (rhIGF-I) (100 μg/kg body wt subcutaneously twice daily) to nine individuals with baseline inulin clearances below 21 ml/min/1.73 m^2. Four patients were treated for four days (short-term treatment) and five for periods between 13 and 27 days (long-term treatment). Administration of rhIGF-I increased inulin clearance, p-aminohippurate (PAH) clearance and the percent tubular reabsorption of filtered phosphate, and decreased plasma creatinine, blood urea nitrogen (BUN) and plasma phosphate during short-term administration. Kidney volume was unchanged in patients receiving the growth factor. rhIGF-I did not cause weight gain, proteinuria or hypoglycemia. Inulin clearance was not increased significantly above baseline after 13 or 20 days of IGF-I administration. PAH clearance remained elevated after 13 days, but not after 20 days of IGF-I. Levels of total circulating IGF-I were elevated above basal levels during the entire course of long-term IGF-I administration. In contrast, levels of circulating IGF binding protein 3 (IGFBP3) declined over time. Side effects related to IGF-I forced discontinuation of its use in two of five patients undergoing long-term treatment, and side-effects possibly related to IGF-I prompted discontinuation of its use in two others. We conclude that rhIGF-I can enhance glomerular filtration rate and renal plasma flow when administered short-term to humans with end-stage chronic renal renal failure. Further studies will be required to define its efficacy and usefulness long-term.

Insulin-like growth factor I (IGF-I) is a proinsulin-like peptide that exerts a variety of actions in the kidney [1]. Infusion of the peptide in humans with normal renal function increases glomerular filtration rate and renal plasma flow [2, 3]. Based upon data generated in models of chronic renal failure in rats, it was thought that the kidney was resistant to the effects of IGF-I to enhance renal function in the setting of reduced functional renal mass. However, we recently demonstrated that humans with moderately-reduced renal function (inulin clearances between 22 and 55 ml/min/1.73 m^2) do respond to short-term (4 days) IGF-I administration by increasing their rates of glomerular filtration and renal plasma flow. Our observations, although preliminary, establish the potential for use of IGF-I as a therapeutic agent in the setting of chronic renal failure [4].

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The present studies were conducted to determine whether the actions of IGF-I that we observed in patients with moderately-reduced kidney function are manifest in individuals with end-stage chronic renal failure. To this end, we administered recombinant human insulin-like growth factor I (rhIGF-I) in a fixed dose (100 μg/kg body wt twice daily) to nine individuals whose baseline inulin clearances were less than 21 ml/min/1.73 m^2, and evaluated its effects on inulin and p-aminohippurate (PAH) clearances, on kidney volume, and on other parameters of kidney function. One group of patients received rhIGF-I for four days (short-term). A second group of patients was to be administered the growth factor for 28 days (long-term). Our data clearly demonstrate that rhIGF-I can increase glomerular filtration rate and renal plasma flow when administered short-term to patients with end-stage renal insufficiency. Furthermore, the growth factor is well-tolerated short-term. To our knowledge, this represents the first demonstration that renal function can be enhanced over a period of days by the administration of a pharmacological agent in the setting of end-stage disease. However, the enhancements of the glomerular filtration rate and renal plasma flow induced by IGF-I short-term do not persist during long-term administration and incidence of side-effects is high. A strategy to tap the potential for use of IGF-I long-term as a therapeutic agent for chronic renal failure remains to be developed.

Methods

Individuals with end-stage chronic renal insufficiency, defined as a creatinine clearance less than 20 ml/min/1.73 m^2, were selected for the study. Patients with polycystic kidney disease, a single kidney or a history of malignancy were excluded from the study. Characteristics of the patients including baseline inulin clearances are shown in Table 1.

The study protocol was approved by the Human Studies Committee of Washington University. Patients were admitted to the Washington University General Clinical Research Center (GCRC) and placed on a 35 kcal/kg/day, 2 g sodium/day 0.8 g/kg/day protein diet. Subjects remained on the standardized diet throughout the duration of the study.

Patients participated in either short-term (4 day) or long-term (28 day) protocols. The first day of the protocols was designated day 0. On day 0, measurements of blood urea nitrogen (BUN), serum Na^+, K^+, HCO_3^- creatinine, calcium and phosphate and 24-hour urinary excretion of calcium, phosphate and protein

Table 1. Patient characteristics

Patient	Age/sex	Diagnosis	Medications	Inulin clearance
1	58M	Membranoproliferative glomerulonephritis	Nifedipine XL Clonidine Furosemide	15.8
2	71F	Hypertension	Verapamil Clonidine Furosemide	7.8
3	59M	Hypertension	Nifedipine XL Captopril Isordil	5.1
4	40F	Systemic lupus erythematosus	Fosinopril Furosemide Prednisone	13.8
5	62M	Diabetes mellitus	Indapamide Nicardipine Furosemide	10.4
6	41M	Nephritis	Nifedipine Pindolol	14.0
7	34M	Henoch-Schönlein Purpura	Nifedipine XL Nadolol	13.8
8	37M	Hypertension	Nifedipine XL Indapamide Furosemide	20.6
9	43F	Chronic glomerulonephritis	Doxazosin Diltiazem Furosemide	10.4
10	73F	Hypertension	Enalapril Amlodopine Coumadin	13.6

were obtained in addition to inulin and PAH clearances and spiral computerized tomographic examinations for determination of kidney volume. On days 1 through 4 for patients enrolled for short-term protocols, or days 1 through 13 to 27 for patients enrolled for long-term protocols, the subjects received rhIGF-I (provided by Genentech Inc., South San Francisco, California, USA) 100 μg/kg subcutaneously twice per day (8 a.m. and 8 p.m.). Inulin and PAH clearances were repeated on one or more occasions during days 2 to 4 and when applicable on days 13, 20 and 27. Measurement of BUN, serum Na^+, K^+, HCO_3^-, creatinine, serum calcium and phosphate, serum IGF-I and IGFBP3, and urine calcium, phosphate and protein were obtained on day 4. Measurements of kidney volume by spiral computerized tomography were repeated on day 4. Blood pressure, and pulse were measured four times daily, and measurement of body weight was performed daily. In addition, blood glucose was measured daily during the period of growth factor treatment.

Patients were discharged from the GCRC following cessation of IGF-I treatment, but remained on the standardized diet. The patients returned 12 to 20 days post-discharge for follow-up inulin and PAH clearances, measurements of BUN, serum creatinine, calcium, phosphate and electrolytes, serum IGF-I and IGFBP3, and spiral computerized tomographic measurements of kidney volume.

BUN, serum Na^+, K^+, HCO_3^-, creatinine, calcium, phosphate and glucose were measured on a Hitachi 747 autoanalyzer (Boehringer Mannheim, Indianapolis, Indiana, USA). Urine calcium and phosphate were measured on a Kodak E700 autoanalyzer (Eastman Kodak, Rochester, New York, USA). Urine proteins were measured on a Technicon RA-XT Analyzer (Indianapolis, Indiana, USA). Glomerular filtration rates and rates of renal plasma flow were estimated by measurements of inulin and PAH clearances as previously described [4]. Data represent the means of three to four separate determinations per study period. Radioimmunoassay for IGF-I was performed in the core laboratory of the Washington University Diabetes Research and Training Center for patients administered IGF-I short-term as previously described [4]. For patients administered IGF-I long-term, IGF-I and IGFBP3 levels in serum were measured by Endocrine Sciences (Calabasas Hills, California, USA). Tubular reabsorption of filtered phosphate was calculated as described previously [4] using data obtained on days 0 and 4, and expressed as a percentage of the filtered load.

Computerized tomographic examinations and calculations of renal volume were performed in the Mallinckrodt Institute of Radiology (Washington University).

Three of the individuals with end-stage chronic renal failure who had previously received IGF-I (patients 6, 7 and 8) and an additional individual (patient 10) were readmitted/admitted to the GCRC under conditions identical to those described above and unknowingly received injections of vehicle for four days instead of IGF-I.

Dunnett's multiple comparison procedure [5] was used for multiple comparisons. Values were considered significantly different if $P < 0.05$ for two-tailed analysis. Data shown in Figure 1 were analyzed using one way analysis of variance (ANOVA) (Instat, Graph Pad Software Inc., San Diego, California, USA).

Results

We have shown previously that administration of 100 μg/kg rhIGF-I, twice daily, to patients with moderate chronic renal insufficiency increases inulin and PAH clearances progressively over a four day period of time [4]. Similar observations were made when rhIGF-I was given short-term to four patients with end-stage chronic renal failure. Figure 1 illustrates clearances expressed as % baseline levels. Baseline inulin and PAH clearances were 10.6 ± 2.5 and 58.7 ± 12 ml/min/1.73 m^2, respectively. Each clearance was increased significantly over four days of IGF-I administration (ANOVA) (Fig. 1). On day 4, inulin clearance (14.0 ± 2.6 ml/min/1.73 m^2) was elevated 32% above baseline and PAH clearance (75.3 ± 17 ml/min/1.73 m^2) was increased 28% compared to baseline levels ($P < 0.05$ for each comparison, Dunnett's multiple comparison procedure). Filtration fractions ranged from 0.19 to 0.21 during days 0 to 4 (Fig. 1).

As was the case for patients with moderate chronic renal failure [4], changes of inulin and PAH clearances in patients with end-stage renal failure were accompanied by parallel changes in levels of circulating IGF-I. During the days on which IGF-I was administered, levels of IGF-I were elevated six- to sevenfold over baseline in the four patients with end-stage chronic renal failure. Following cessation of IGF-I administration, inulin and PAH clearances returned to levels that were not different from baseline (Fig. 1) as before [4].

Administration of vehicle for four days to four patients with end-stage chronic renal failure did not increase inulin or PAH clearances. Values for inulin clearance were 16.5 ± 2.1 and 13.0 ± 1.6 ml/min/1.73 m^2, respectively, on days 0 and 4 and values

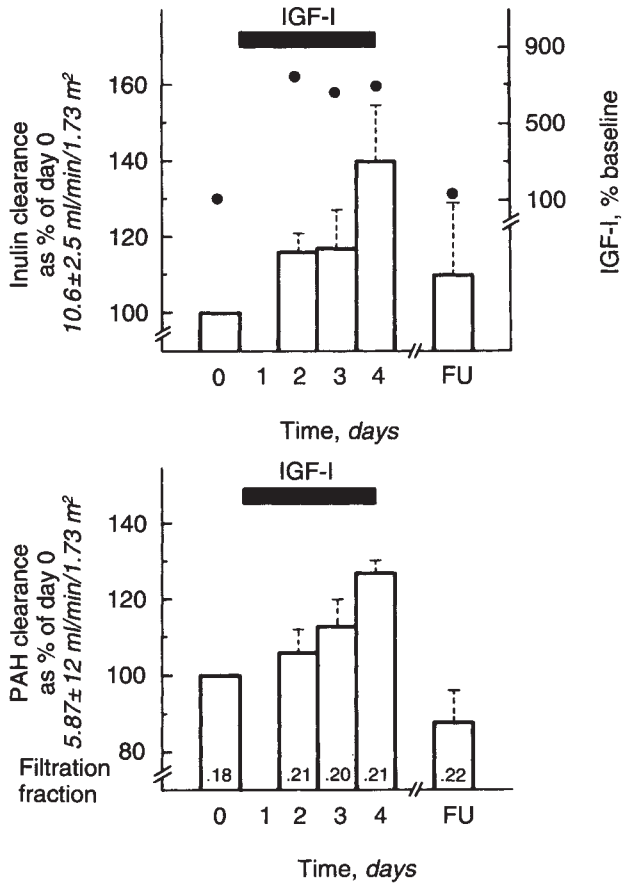

Fig. 1. A. *Inulin clearances (vertical bars) and levels of serum IGF-I (●) measured over time in patients 1 to 4.* The time of administration of IGF-I is indicated by the closed horizontal bar. Inulin clearances are expressed as mean ± SE. Levels of IGF-I on day 0 were 0.8 ± 0.2 U/ml. **B.** PAH clearances (vertical bars) and filtration fractions (shown at bases of vertical bars) in patients 1 to 4. PAH clearances are the means ± SE. FU (follow-up).

Table 2. Effect of IGF-I on inulin and PAH clearance and serum parameters

Parameters (patients 1-9)	Pre	Rx	Post
Inulin clearance *ml/min/1.73 m²*	13.3 ± 1.5	16.4 ± 1.7[a]	12.5 ± 1.3
PAH clearance *ml/min/1.73 m²*	59.1 ± 9.8	76.0 ± 13[a]	57.1 ± 11
Serum Na^+ *mg/dl*	139 ± 1.2	138 ± 1.1	139 ± 1.5
Serum K^+ *mg/dl*	4.2 ± 0.2	4.1 ± 0.2	4.4 ± 0.2
Serum HCO_3^- *mEq/liter*	19.8 ± 1.3	20.4 ± 1.0	20.4 ± 1.0
BUN *mg/dl*	78.7 ± 4.9	62.5 ± 5.0[a]	75.5 ± 5.5
Serum calcium *mg/dl*	8.8 ± 0.3	9.2 ± 0.2	8.9 ± 0.4
Serum creatinine *mg/dl*	6.9 ± 0.6	6.1 ± 0.3[a]	6.9 ± 0.6
Serum phosphate *mg/dl*	5.0 ± 0.3	4.5 ± 0.3[a]	5.2 ± 0.4

Values were obtained on day 0, prior to IGF-I administration (Pre), on day 4, during IGF-I administration (Rx), and post-discharge from the GCRC (Post).

[a] Different from day 0, $P < 0.05$, Dunnett's multiple comparison procedure

Table 3. Effect of IGF-I on urine parameters

Parameter (patients 1–9)	Pre	Rx
Urine Volume *ml/24 hr*	3374 ± 354	3174 ± 353
Urine calcium *mg/24 hr*	44 ± 13	39 ± 9
Urine phosphate *mg/24 hr*	569 ± 107	468 ± 71
% Tubular reabsorption of filtered phosphate	47.2 ± 4.5	60.8 ± 3.8[a]
Urine protein *mg/24 hr*	2558 ± 817	2734 ± 1174

Values were obtained on day 0, prior to IGF I administration (Pre) or on day 4, during IGF I administration (Rx).

[a] Different from day 0, $P < 0.0005$, Student's *t*-test

for PAH clearance were 75.3 ± 23 and 67.8 ± 16 ml/min/1.73 m^2, respectively.

Measurements of inulin and PAH clearance, BUN, serum Na^+, K^+, HCO_3^-, calcium, creatinine and phosphate were obtained on a total of nine patients who received at least four days of IGF-I treatment (patients 1 to 9). Values obtained prior to treatment (Pre) were compared with those obtained following four days of treatment (Rx) and those obtained 12 to 20 days following cessation of IGF-I administration (Post). Treatment with 100 μg/kg rhIGF-I twice daily increased significantly inulin and PAH clearances and decreased signficantly BUN, serum creatinine and serum phosphate measured on days 4 compared to values measured on day 0, consistent with improvement of renal function. Serum HCO_3^-, and calcium were not changed significantly. All values did not differ significantly from baseline (day 0) when measured following cessation of IGF-I (Table 2).

Urine volume, calcium, phosphate and protein were not significantly different on day 4 (Rx) of IGF-I administration from values measured on day 0 (Pre). The percent tubular rebsorption of filtered phosphate was significantly increased as before [4] (Table 3).

Kidney volumes measured by spiral computerized tomography on day 0 (289 ± 45 cm^3), day 4 (288 ± 40 cm^3) and following cessation of IGF-I treatment (258 ± 41 cm^3) did not differ significantly, one from the other.

Side effects of IGF-I experienced by patients 1 to 4 are listed in Table 4. In none of these patients was any side effect of sufficient severity to result in discontinuation of the growth factor.

Five patients (patients 5 to 9) were enrolled in long-term studies designed to delineate the effects of rhIGF-I administered for 28 days. Baseline inulin and PAH clearances in these five patients were 14.1 ± 1.7 and 59.4 ± 16 ml/min/1.73 m^2, respectively. The results of the long-term studies are shown in Figure 2 which illustrates inulin and PAH clearances expressed as the percent of baseline values. Only one of five patients enrolled was able to complete a 28 day course of rhIGF. Growth factor administration was discontinued because of side effects in four others (discussed below). One patient (patient 5) who lived outside of the St. Louis metropolitan area returned home following cessation of IGF-I treatment to the care of his referring physician, and was not able to return for follow-up studies. A total of five patients received IGF-I for 13 days, three

Table 4. Side effects of IGF-I

Patient number	Side effect	Days encountered	Day resolved	IGF-I discontinued
1	None			No
2	Jaw pain	3–4	5	No
3	None			No
4	Jaw pain	2–4	5	No
5	Nasal congestion	8–20	22	Yes
	Pericardial rub	20	22	
6	Nasal congestion	4–27	28	No
	Jaw pain	6–15	16	
7	Bell's palsy	20	27	Yes
8	Nasal congestion	7–15	17	Yes
	Jaw pain	13–15	17	
	Gingival Hypertrophy	12–15	30	
9	Nasal congestion	4–13	15	Yes
	Pericardial rub	13	15	

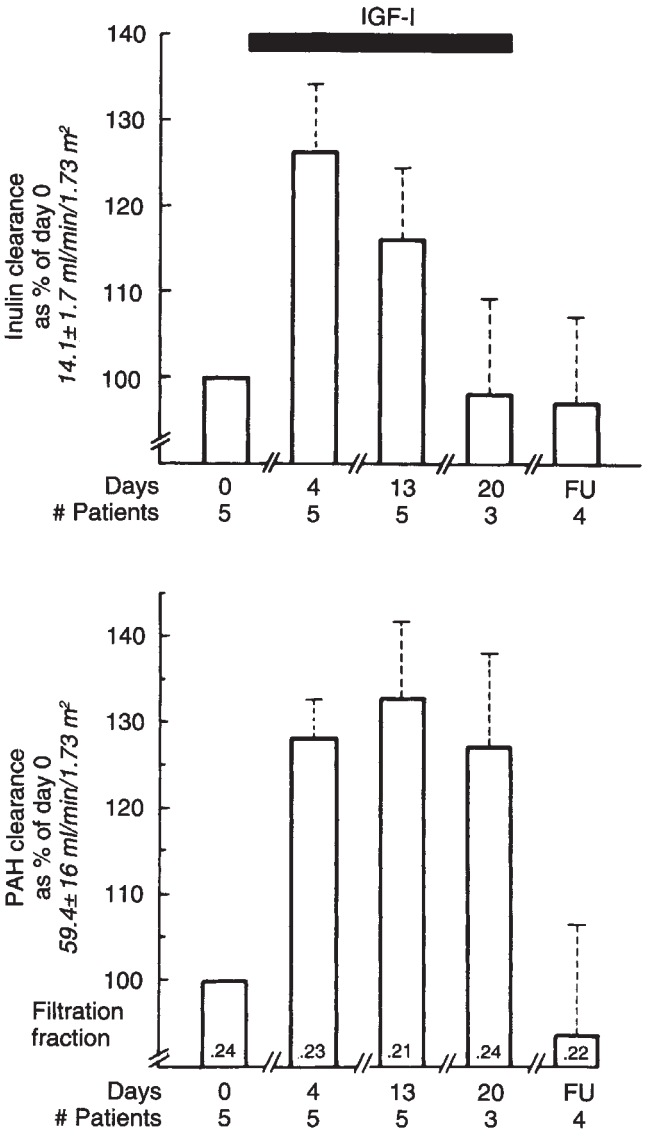

Fig. 2. *(A) Inulin clearances, (B) PAH clearances and filtration fractions measured over time in patients 5 to 9.* The number of patients remaining in the study over time (# patients) is shown. Data are expressed as in Figure 1.

for 20 days and one for 27 days. Follow-up studies were performed on four patients.

On day 4, inulin clearances (17.9 ± 2.6 ml/min/1.73 m^2) were elevated significantly above those measured on day 0 ($P < 0.05$, Dunnett's multiple comparison procedure). However, inulin clearances on day 13 (16.7 ± 2.5 ml/min/1.73 m^2) were no longer elevated significantly, and those measured in the three patients remaining in the study on day 20 were not significantly different from inulin clearances measured in the same patients on day 0 (12.7 ± 2.7 vs. 12.7 ± 1.2 ml/min/1.73 m^2, respectively).

PAH clearances measured on day 4 (78.6 ± 24 ml/min/1.73 m^2) were not elevated significantly above those measured on day 0 for patients 5 to 9. However, PAH clearances were elevated significantly above baseline for all nine patients (Table 2). PAH clearances measured on day 13 (80.0 ± 22 ml/min/1.73 m^2) were significantly greater than those measured on day 0 ($P < 0.05$, Dunnett's multiple comparison procedure). However, PAH clearances measured for the three patients remaining in the study on day 20 were not significantly different from values obtained for those three patients on day 0 (52.8 ± 9.4 vs. 41.3 ± 5.9 ml/min/1.73 m^2, respectively). Only patient 6 remained in the study on day 27. His inulin and PAH clearances on that day (14.0 and 52.0 ml/min/1.73 m^2, respectively) were 100% and 140% of his baseline values. Inulin clearances measured on day 0 and at follow-up for the four patients who completed the long-term study (14.0 ± 1.1 vs. 15.0 ± 1.9 ml/min/1.73 m^2, respectively) were not significantly different. Similarly, PAH clearances measured at these times did not differ (65.0 ± 19 vs. 63.7 ± 21 ml/min/1.73 m^2, respectively). Filtration fractions ranged from 0.21 to 0.24 during days 0 to 20 (Fig. 2).

Levels of circulating IGF-I measured in patients 5 to 9 were elevated significantly above baseline on days 4, 13 and 20 ($P < 0.01$, $P < 0.01$, and $P < 0.05$, respectively, Dunnett's multiple comparison procedure). Levels measured on day 13 were not significantly different from those measured on day 4. However, levels measured on day 20 were lower than those measured on day 4 ($P < 0.05$, Dunnett's multiple comparison procedure). Levels measured at the time of follow-up studies were not different from those measured on day 0. Levels of circulating IGFBP3 measured on days 4, 13, and 20 were reduced significantly from those measured on day 0 ($P < 0.01$, $P < 0.01$ and $P < 0.05$, respectively, Dunnett's multiple comparison procedure). Levels of IGFBP3 measured at the time of follow-up studies were not different from those measured on day 0 (Fig. 3). Circulating IGF-I and IGFBP3 levels in patient 6 were 236% and 53% of his baseline values, respectively, on day 27.

All side-effects of rhIGF-I that were encountered in patients 1 to 9, the day on which they were first reported, and the day on which they resolved are listed in Table 4. Nasal congestion and pain at the angles of the jaw (jaw pain) were the most frequent side effects of IGF-I (4 of 9 patients each). Neither side effect was of sufficient severity so that, in our judgment, administration of the the growth factor needed to be discontinued. Jaw pain resolved in patients 6 and 8 while they continued to receive IGF-I. In the other patients who developed jaw pain and in the patients who developed nasal congestion, these side effects

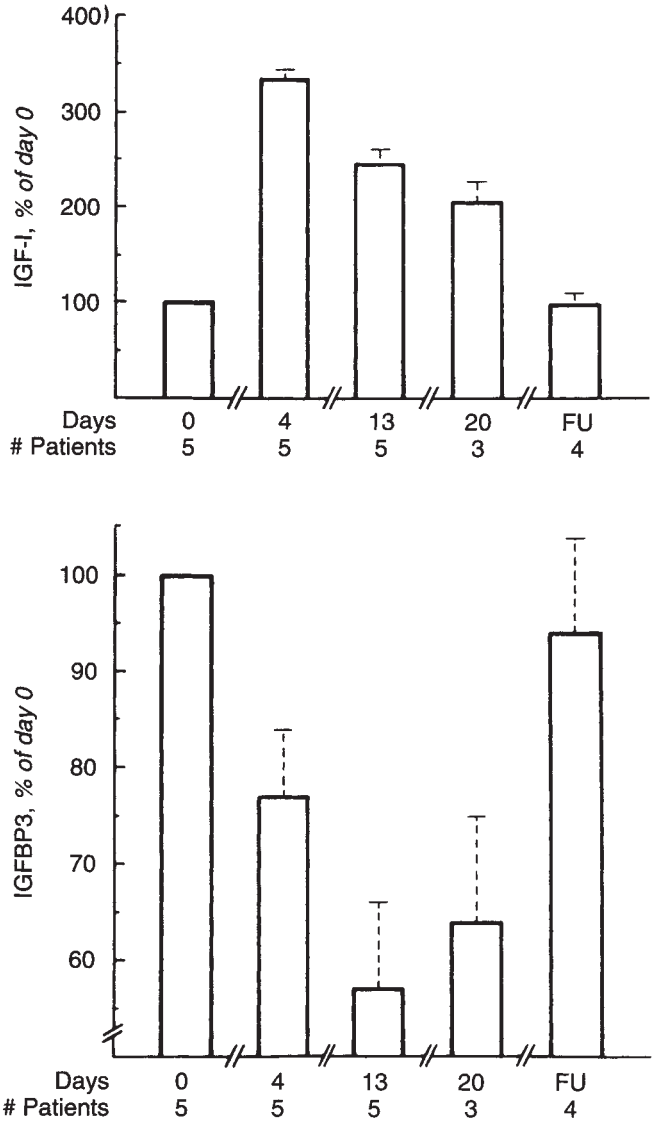

Fig. 3. *Levels of total circulating IGF-I (A) and IGFBP3 (B) measured over time in patients for whom data are shown in Figure 2.* Data are expressed as mean ± SE. Levels of IGF-I and IGFBP3 on day 0 were 192 ± 13 ng/ml and 3.5 ± 0.2 mg/liter, respectively.

resolved within two days of discontinuation of the growth factor. More serious side effects of IGF-I that did prompt discontinuation of the growth factor were development of Bell's palsy (patient 7) and gingival hypertrophy (patient 8). The Bell's palsy was completely resolved by seven days after stopping IGF-I. Gingival hypertrophy was no longer present 15 days after IGF-I was discontinued. Patients 5 and 9 developed pericardial friction rubs during the course of IGF-I treatment. We cannot be certain whether they were related to IGF-I or to end-stage renal failure. At the time the rubs were noted the inulin clearance of patient 5 was 8.0 ml/min/1.73 m^2 and of patient 9 was 13.4 ml/min/1.73 m^2. Therefore each could be considered uremic. No patient experienced hypoglycemia, alterations in blood pressure, heart rate or experienced any cardiac arhythmia at any time during the study. There were no seizures, and margins of optic discs remained sharp during the course of IGF-I administration to every patient.

Discussion

It has been shown that continuous subcutaneous IGF-I administration increases glomerular filtration rate and renal plasma flow in humans with normal renal function [2, 3], and enhances glomerular filtration rate and renal plasma flow in patients with moderately-reduced renal function [4]. However, to our knowledge, ours is the first demonstration that IGF-I increases glomerular filtration rate and renal plasma flow in humans with end-stage chronic renal insufficiency. The mean percent increase in glomerular filtration rates observed in nine patients with end-stage chronic renal insufficiency following four days of IGF-I administration (23%) is comparable to that observed in humans with normal renal function (29 to 30%) [2], despite the administration of a higher dose of IGF-I to individuals with normal kidney function (480 μg/kg/day for 6 days) than to patients with kidney failure (200 μg/kg/day for 4 days). The increments in levels of circulating IGF-I that resulted from administration of IGF-I to humans with normal renal function (6- to 7-fold elevation) [2], were similar to those measured in the patients with end-stage chronic renal failure (Fig. 1 and 3). Therefore, on the basis of comparing the response in normal humans [2, 3] and in patients with end-stage chronic renal failure, there is no evidence of renal resistance to the action of IGF-I to enhance glomerular filtration rate or renal plasma flow when administered short-term in the setting of severely-reduced functional kidney mass. This is different from the resistance to the action of GH [6, 7]. It is clear that renal functional reserve remains in the setting of severe loss of renal function and that the potential exists for the increase of the glomerular filtration rate by medical means.

The studies of long-term IGF-I administration to patients with end-stage chronic renal failure that are included in the present report were conducted to ascertain whether the effects of IGF-I to increase inulin and PAH clearances short-term (Fig. 1) are observed during longer-term IGF-I administration. Neither the action of IGF-I to enhance inulin clearance nor its action to increase PAH clearance was manifest long-term (Fig. 2). Lack of persistence might be be explained by falling levels of total circulating IGF-I (Fig. 3).

The dynamics of IGF-I interaction with sensitive tissues are complex and incompletely understood. Biological activity of circulating IGF-I is regulated by levels of plasma IGFBPs which both enhance and inhibit IGF-I actions [8, 9]. In addition, IGFBPs present in tissues regulate the interaction of circulating IGF-I with its receptor. Tissue IGF-I receptor density is altered by changes in levels of circulating IGF-I. In kidney, numbers of IGF-I receptors are inversely related to levels of circulating IGF-I [10].

Administration of rhIGF-I to patients with normal renal function [9] or end-stage chronic renal failure (Fig. 3) results in changes in at least one component of the IGF-I effector system (reduced IGFBP3). It is possible that the lack of persistence of the action of IGF-I to enhance glomerular filtration rate represents a refractoriness to IGF-I that results directly from this change. Alternatively, the reduction in levels of circulating IGFBP3 may reflect alterations in other components of the

effector system such as down-regulation of renal IGF-I receptors.

It is known that under some circumstances elevated levels of circulating IGF-I are associated with or directly causative of long-term changes in renal function. For example, the enhancements of inulin and PAH clearances that accompany the elevations of circulating GH and IGF-I in patients with acromegaly are sustained over years of time [11]. An increase in creatinine clearance occurred within the first 12 days of IGF-I administration to a GH-insensitive Laron dwarf. The increase was progressive over the next 59 days [12].

GH stimulates the synthesis of IGFBP3 in liver [1, 8, 9]. It is the reduction in levels of circulating GH resulting from IGF-I inhibition of pituitary GH release that is thought to result in the fall of circulating IGFBP3 in humans administered IGF-I. Concomitant administration of GH and IGF-I has been shown to prevent the fall in circulating IGFBP3 and to enhance the anabolic effects of each agent administered alone to humans [9]. Similarly, the combination of elevated GH and IGF-I levels in acromegaly could permit the growth factor to enhance renal function long-term by sustaining levels of IGFBP3 or modifying some other component of the IGF-I effector system. Because of their GH insensitivity, IGFBP3 levels are low and are increased by IGF-I in Laron dwarfs [13]. This difference or another difference in the IGF-I effector system could explain the absence of refractoriness to IGF-I in these individuals.

It may be possible to prolong the duration of the increase in inulin and PAH clearance induced by IGF-I by altering the dosage of IGF-I or the timing of its administration so as to prevent the change in levels of circulating IGF-I or in the effector system. Alternatively, co-administration of GH with IGF-I may reduce or eliminate the refractoriness that occurs over time (Fig. 2).

The administration of IGF-I to experimental animals or to humans has been reported to result in several side effects. Hypoglycemia is dose-related [9] and was not observed in our study. Tachycardia is a recognized side effect of IGF-I [14] and was seen in association with its administration in one patient with moderately-reduced renal function [4], but in none of the patients included in the present study. Side effects of IGF-I reported in other studies include Bell's palsy [15], papilledema [15], hypokalemia [15], and pain at the angle of the jaw [12, 14], some of which our patients suffered (Table 4). As is the case for hypoglycemia, the incidence of other side effects of IGF-I may be reduced by decreasing the dose [9, 16].

Administration of rhIGF-I to indivduals with end-stage chronic renal failure resulted in neither fluid retention nor proteinuria. In contrast to the findings of Walker, van Wyk and Underwood [12], rhIGF-I did not increase urinary calcium excretion or urinary volume. As would be expected from its effect to enhance the transport of phosphate across the proximal tubular brush border membrane [17], rhIGF-I increased the percent tubular reabsorption of phosphate (Table 3). However, hyperphosphatemia was not observed (Table 2).

One potential risk that could accompany the therapeutic use of IGF-I in chronic renal failure is that of glomerulosclerosis resulting from the hyperfiltration induced by this agent. Caution is clearly indicated regarding its use in patients with dramatically reduced renal function whose nephrons are already hyperfiltrating. Indeed, the decline in inulin and PAH clearances that occurred following the initial increases after initiation of IGF-I administration could be the result of hyperfiltration.

Evidence that growth-promoting agents may be glomerulosclerotic comes from studies of rodent models of hypersomatotropism. Hypersomatotropic rats [18] and mice transgenic for GH [19, 20] develop glomerulosclerosis. However, it is of interest that mice transgenic for IGF-I with levels of circulating IGF-I comparable to those in mice transgenic for GH do not develop glomerulosclerosis [19, 20]. This finding is consistent with the glomerulosclerotic action of GH in rodents being mediated via a mechanism other than its action to increase the synthesis and release of IGF-I.

Additional support for the safety of IGF-I or GH administration in humans may be derived from the observation that, in contrast to the case in rodents, chronic renal failure is not a complication of hypersomatotropism in humans. In fact, patients with long-standing acromegaly manifest marked renal hypertrophy and have supranormal glomerular filtration rates, suggesting that the hyperfiltration that accompanies long-standing elevations of circulating GH and IGF-I in humans is not injurious to the kidney [11, 21].

Appendix. Abbreviations

ANOVA, analysis of variance; BUN, blood urea nitrogen; FU, follow-up; GCRC, general clinical research center; GH, growth hormone; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; PAH, p-aminohippurate.

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